The Genetics and Comorbidity of Migraine

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Summary & General Discussion

The research described in this thesis focuses on the definition and etiology of migraine in large population based studies. A variety of methods were applied in this work. To optimize the definition of the migraine phenotype, we applied latent class analysis to data collected in survey studies. Genetic modelling of twin data was applied to examine the comorbidity of migraine with depression and the heritability of migraine as a function of depression status. Finally, linkage and genome-wide association studies were performed to localize and identify genetic variants potentially involved in migraine. In this chapter, I first provide a summary of the main results followed by a discussion of the implications of this work. I conclude with an outline of recommendations for future research.

SUMMARY

INTRODUCTORY CHAPTERS

In the first chapter of this thesis, an overview is provided of the literature on the epidemiology and pathophysiology of migraine. The chapter describes how migraine is currently diagnosed, what is known about the mechanisms underlying a migraine attack, and how migraine is associated with several psychiatric and non-psychiatric conditions. In addition, the chapter provides a summary of the most important results from migraine gene-finding studies, which are primarily based on studies of *familial hemiplegic migraine*, a rare and severe monogenic subtype of migraine with aura. Three genes have been implicated in this disorder, all of which are involved in ion transport. For common migraine, several linkage and candidate-gene association studies have been performed, but a causal genetic variant has not been identified. The chapter ends with an outline of the research described in this thesis. Important aims were to investigate the genetic architecture of migraine and comorbid depression, and to identify the genes underlying migraine.

Chapter 2 provides an overview of the methods employed in genetic epidemiology to address these issues. These methods include the genetic modelling of twin and family data, genetic linkage studies in family data, genome-wide association studies in (unrelated) cases and controls and meta-analysis of the results of such studies,

Chapters 3 and 4 describe the data collection procedures in the Netherlands Twin Register (NTR) that preceded the studies described in this thesis, and provide some background information on the samples analyzed. In Chapter 4, it was investigated whether there was any evidence for non-random participation in the surveys of the NTR. This study concluded that there was no evidence of a response bias with respect to migraine status.

ANALYSES OF THE MIGRAINE PHENOTYPE AND COMORBIDITY WITH DEPRESSION

Chapters 5-7 focused on the analysis of the migraine phenotype by analyzing the symptoms of migraine, as defined by the official diagnostic criteria (IHS; Headache Classification Committee of the International Headache Society, 2004), the comorbidity of migraine and depression and the moderation of the heritability of migraine by depression. Data on migraine and depression were collected with mailed surveys in large samples of NTR participants. Additional

data on major depressive disorder from the Netherlands Study of Depression and Anxiety (NESDA; Penninx et al., 2008) were included in Chapter 6.

In Chapter 5, migraine symptoms were analyzed with latent class analysis (LCA) to investigate whether there was any evidence for distinct subtypes of migraine. One important question was whether distinct classes would be characterized by the presence or absence of aura symptoms. The LCA empirically identified 4 classes of individuals, based on migraine symptomatology. The results were very similar for males and females, indicating that although the prevalence is higher in females, there are no qualitative sex differences in migraine symptomatology. The frequency of aura symptoms was not a particularly distinctive feature that characterized any of the groups. The observed pattern showed that what distinguished the classes was the severity of the migraine and the number of symptoms reported, rather than qualitative differences. The only qualitative difference between the classes was that the increase in symptom prevalences in class 3 compared to class 2 was relatively stronger for the symptoms *photo-/phonophobia*, *nausea/vomiting*, and *aura*, reflecting the fact that these symptoms are relatively rare in mildly affected patients. But even in the most severely affected group (class 3) only 49% of the patients had aura. In this study, the heritability of the LCA-based phenotype was estimated at 50%, which is comparable to the heritability of migraine according to IHS-criteria (49%). Due to the low number of dizygotic male twin pairs screening positive in the sixth survey, the heritability estimates reported in Chapter 5 were based on data from women only. In Chapter 7, the heritability of LCA-derived migraine was estimated at 45%, based on data from both women and men.

In summary, the results indicate that no distinct group of MA patients can be identified based on symptomatology. This is consistent with the results of an earlier study in Australian twins (Nyholt et al., 2004), and suggests a similar disease process may underlie MO and MA. The results of this chapter support the use of a broad, LCA-based phenotype in genetic studies of migraine, and the combined analysis of data from patients with MO and MA. This results in a larger number of individuals classified as affected, and thus maximizes power to detect genetic effects. In the gene-finding studies described in Chapter 8 and 9, this strategy was continued.

In Chapter 6 migraine symptomatology in MDD patients and non-depressed controls was compared using a similar LCA-based approach. It is known that migraine has a higher prevalence in depressed patients (Breslau et al., 2000; Merikangas et al., 1988). However, the diagnostic criteria allow a

substantial heterogeneity of specific symptoms between individuals (i.e., many different combinations of symptoms can result in the same endpoint diagnosis). Therefore it is important to know whether we are indeed observing the same disorder in depressed and non-depressed individuals. Because certain symptoms are more prevalent in patients with severe migraine (Chapter 5), a higher prevalence of severe migraine in MDD patients might be mistaken for a qualitative difference in migraine symptomatology, for instance because MDD patients more often have photo-/phonophobia or aura. For this reason, we examined whether there were qualitative differences, while taking differences in prevalence and severity into account. This was achieved by performing a multi-group latent class analysis, in which symptom profiles were estimated in MDD-patients and non-depressed controls. It was formally tested whether the same symptom profiles were observed in the MDD patients and the controls.

The data confirmed that the prevalence of severe migraine was much higher in the MDD patients. However, qualitative differences between the symptom profiles of MDD patients and controls were only minor: the symptoms aggravation by physical activity and aura both had a slightly higher prevalence in the MDD group, for the other symptoms no significant differences were found between the two groups. These results suggest that a similar disease process may underlie migraine in individuals with and without MDD. However, a similar symptomatology does not prove that the etiology of the disorder is the same. Thus, while there is migraine is qualitatively similar in depressed and non-depressed individuals, we should be cautious in assuming the same etiology in both groups.

In Chapter 7 we took the investigation of migraine and comorbid depression one step further and examined 1) the genetic and environmental correlation between migraine and anxious depression, 2) the genetic architecture of migraine in individuals with high and low anxious depression scores, and 3) tested whether the association is more likely explained by causality or by shared underlying genes (pleiotropy). Firstly, the heritability estimates for migraine and depression were 45% and 55%, respectively, and a bivariate genetic model showed that the two traits were indeed genetically correlated. The non-shared environmental factors (which explained the remaining variance in both traits) were also correlated. Secondly, a test of the moderating effects of depression on the heritability of migraine, revealed that migraine was more heritable in individuals with low anxious depression scores. Thirdly, in MZ twin pairs discordant for migraine, the twin without migraine did not have an increased risk of depression, and vice versa. In other words, the fact

that the first twin had migraine, did not increase the risk that the second twin had depression, unless the second twin also had migraine (and vice versa). If there was no causality, it would be expected that the MZ co-twin without migraine had the same risk of depression as the twin with migraine, because they share the same genes. These results suggest that the association between migraine and anxious depression is most likely explained by bidirectional causality.

Gene-finding studies

Given the heritability of migraine, a logical next step is to try and identify the genes that underlie the disorder. This work is summarized in Chapters 8 and 9, which describe linkage and genome-wide association studies for migraine. Following from the results of Chapter 5, linkage and genome-wide association analyses these studies were performed using the LCA-based classification of migraine, in order to maximize the power to detect migraine susceptibility genes.

In the linkage study described in Chapter 8 three linkage peaks were identified that surpassed the threshold for suggestive linkage, on chromosome 1q23, 13q32 and 20p12. The finding on chromosome 1 was particularly interesting because it was located only 5 cM away from the ATPase, Na+/K+ transporting, alpha 2 polypeptide *(ATP1A2)* gene, which is involved in familial hemiplegic migraine. In addition, some smaller linkage peaks were identified, which replicated previous findings on chromosome 5q21 (Nyholt et al., 2005) and 10q22 (Anttila et al., 2006; Nyholt et al., 2005). Interestingly, the peak on chromosome 20 was recently replicated in a linkage study of bipolar disorder and comorbid migraine in families from the NIMH Bipolar Genetics Initiative, where it was linked to both migraine and bipolar disorder (Oedegaard et al., 2009).

Chapter 9 describes the results of a meta-analysis of genome-wide association studies for migraine in six samples of European ancestry (five Dutch samples and one Icelandic). The best result in this study was found for a SNP on chromosome 17, located in the *NGFR* gene. This gene codes for the neural growth factor (NGF) receptor, which plays an important role in pain transmission and sensitization. NGF is upregulated in many chronic pain conditions (Pezet & McMahon, 2006) and has been associated with headache in studies that showed altered cerebrospinal fluid and platelet levels of NGF in headache patients (Blandini et al., 2006; Sarchielli et al., 2001). However, the NGF receptor has not been implicated in migraine etiology before. The results

of the meta-analysis were also compared to previous linkage and association studies, which revealed the possible involvement of *ATP1A2* (one of the genes that causes FHM) and the glutamate receptor, ionotropic, delta 2 *(GRID2)* gene in common migraine. The latter is an interesting candidate because it is located in a region on chromosome 4q22 that has been reported in several independent linkage studies (Anttila et al., 2006; Bjornsson et al., 2003; Oedegaard et al., 2009; Wessman et al., 2002). Glutamate is thought to play an important role in migraine, possibly because high extracellular levels of glutamate can facilitate cortical spreading depression, the mechanism that underlies migraine aura (Sanchez-Del-Rio et al., 2006; van den Maagdenberg et al., 2007).

DISCUSSION

MIGRAINE ASSESSMENT

The assessment of migraine in most studies in this thesis is based on survey data. In large population based studies, assessment of each individual participant by a neurologist (generally perceived to be the 'gold standard' for migraine diagnosis) is not feasible due to financial and time constraints. Genetic studies require large samples and survey-based assessment is a good alternative method that allows the phenotyping of large numbers of participants, so that large-scale genetic epidemiological studies become feasible.

The survey used to assess migraine (Table 3.2) has been described extensively in Chapter 3. It includes items on eight of the symptoms that are included in the official diagnostic criteria (Headache Classification Committee of the International Headache Society, 2004). As described in Chapter 3, the test-retest reliability of the headache items was good, with high correlations between survey 6 and 7 (.82 - .87 for the different items), and also between the first wave of survey 7 (November 2004) and a shortened version of the survey sent to a selected group of participants in July 2005 (correlations .82 - .92). A limitation of the questionnaire was that no question on unilaterality of the headache was included. In addition, photo-, phono-, and osmophobia were combined into one question. To approximate an IHS diagnosis, we considered the C criterion (see Table 1.1) valid only if two out of the three measured C-items (moderate/severe pain intensity, pulsating quality and aggravation by physical activity) were present, which is more stringent than the official requirement (two out of four). The photo- and phonophobia requirement was less stringent

than the official criteria specify. The overall prevalence estimates of IHS migraine in our sample (4% in males, 13% in females) are slightly lower than what is found in other studies based on IHS criteria (e.g., Stewart et al., 1992), suggesting that, due to our relatively strict definition, the prevalence of IHS migraine was underestimated. The number of false positive diagnoses based on this definition is most likely limited.

Classification of participants with Latent Class Analysis

Latent class analysis was applied to investigate whether subgroups of migraine patients could be identified, and whether separate MO and MA subtypes existed. The result was a classification in which the different subtypes differed primarily in terms of severity of the migraine headaches. Class 0 is the group of unaffected individuals, class 1 individuals have mild, non-migrainous headaches, class 2 can be described as moderate migrainous headache, and the individuals in class 3 have severe migrainous headache.

In the gene-finding studies that followed (Chapters 8 and 9), both class 2 and class 3 individuals were classified as migraineurs, which resulted in a high prevalence of migrainous headache (13% in males, 35% in females). As I have argued in previous chapters, using a broad phenotype definition has the advantage that more potentially genetically informative individuals are classified as affected, which increases the power to detect genetic effects. But does a broader definition still reflect migraine, or does it result in the inclusion of other types of mild headache as well?

First, as shown in Chapter 8, the heritability of migraine based on LCA ('LCA migraine'; $h^2 = 49\%$) is approximately the same as the heritability of migraine according to ICHD-II criteria ('IHS migraine'; $h^2 = 46\%$). This indicates that by using the broader phenotype, we do not lose any genetic information. In an Australian study that applied the same method, the heritability of LCA and IHS migraine were also similar, although slightly lower than in our study (40% and 36%, respectively). These estimates are similar to what is generally found for migraine. For example, a study of almost 30,000 twins from six European countries estimated the heritability of migraine at 46% (Mulder et al., 2003).

Second, in the linkage study (Chapter 8), we observed that when we used IHS migraine or 'LCA-severe' (i.e. class 3) as the phenotype, linkage peaks detected with the phenotype based on LCA class 2 + 3 generally became smaller. The use of a stricter definition did not identify any peaks that had not been detected using the more liberal LCA definition (see Figure 8.2). The GWA

analyses for Chapter 9 were also conducted with both IHS and LCA migraine as the phenotypes. The associations detected with the LCA phenotype were still present when using the IHS migraine phenotype, but in general, the p-values were markedly less significant. No strong association signals were observed that emerged only when using the more stringent IHS phenotype.

Clearly, the fact that using a more stringent phenotype reduces the number of cases largely explains the finding that using LCA migraine as the phenotype produces better results. However, if the LCA migraine phenotype were a mixture of migraine and a different type of 'general, undefined headache', one would expect an increase in genetic heterogeneity that would be unlikely to result in more significant association signals than a strict IHS migraine phenotype. This strengthens my confidence that by using the broad LCA phenotype, we indeed measure a genetic risk of migraine. In addition, it is always possible to check the validity of findings based on LCA migraine by repeating the analysis in the subset of individuals fulfilling strict IHS criteria for migraine. In summary, our results indicate that LCA-based classification is a valuable method for large-scale population based genetic studies of migraine, where power and sample size are generally the limiting factors.

Screening procedure

To lower the burden for participants, it is common to start a questionnaire with a screening question, and ask the participant to complete the remaining questions only if these are relevant given the outcome of the screening question. In our migraine questionnaire, the screening question was "Do you ever experience headache attacks, for instance migraine?". Approximately 30% of participants screen positive, based on this question. Thus, with no other information present, we have to assume that the remaining 70% never have headache attacks. This is a high percentage compared to, for instance, a similar study by Nyholt et al. (2004; see also Chapter 5). However, it is possible that due to the phrasing of the question, individuals with mild headaches will think their condition (which does not compare to a severe condition like migraine) does not qualify to even be mentioned. Also, headaches that do not occur attack-wise might go unnoticed with this type of screening. This may explain why latent class 1 had a relatively low prevalence under the 4-class LCA model (Chapter 5); many individuals with this mild type of headache may have screened negative. On the other hand, this also indicates that individuals with moderate or severe migrainous headache (which is our primary interest) are unlikely to screen negative.

A consequence of the use of screening questions is that the collected data are essentially censored, and that there may be some individuals in the 'unaffected' group who have a minor genetic risk of headache. These individuals are not ideal controls, because they are not entirely unaffected.

In the linkage study (Chapter 8), the screening procedure was not an issue, because in this study an affected sib-pair design was used. Thus, the results were based only on individuals we were quite confident were affected, and not on controls who might potentially carry a minor genetic risk of migraine. In the GWA study described in Chapters 9, the unaffected individuals were included as controls. In these studies, we treated the class 1 individuals as unaffected, based on the fact that on average, the majority of migraine symptoms were not reported by this group. To assess the potential implications of treating individuals with mild, non-migrainous headaches as controls, we performed an additional analysis in the GAIN sample, in which the phenotypes of the class 1 individuals were set to missing rather than unaffected. This analysis produced very similar results, suggesting the effect of the potential presence of migraine risk genes in these individuals is limited, if present.

The relationship between migraine and depression

In Chapters 5 and 6, no distinct subtypes of migraine were identified, relating to the presence of aura or major depression. The subtypes identified with latent class analysis do not show major qualitative differences but differ primarily in terms of severity. Does this mean there is only one type of migraine? At the phenotypic level, this appears to be the case. However, at the genetic level, there may be differences between groups of patients. Evidence for this hypothesis comes from Chapter 7. In this chapter, migraine was found to be more heritable in non-depressed than in depressed individuals. In addition, risk patterns in relatives of patients with migraine and anxious depression suggested bidirectional causality. If migraine can be causally related to anxious depression in some patients, this could indicate it is genetically different from migraine unrelated to depression.

Interestingly, Merikangas et al. (1993) reported a similar finding concerning risk patterns in relatives of migraine patients. In this study, after controlling for comorbidity, the relatives of probands with migraine had no increased risk of depression, and vice versa. These results were consistent with causality, rather than shared underlying genes (pleiotropy), and the authors suggested that migraine and depression might be syndromically related.

Since this publication, many studies have confirmed that migraine and depression are correlated (e.g., Beghi et al., 2007; Breslau et al., 2000; Mitsikostas & Thomas, 1999; Zwart et al., 2003), and several authors hypothesized that shared genes might be involved (Breslau et al., 1991; Cahill & Murphy, 2004; Frediani & Villani, 2007). However, only few studies actually addressed the underlying mechanisms that might explain the association.

Breslau et al. (2000) published a study which reported a bidirectional relationship between migraine and depression. Migraine predicted first-onset major depression and major depression predicted first-onset migraine. This relationship was specific to migraine: depression did not predict the first onset of other severe headaches.

In 2009, the first twin study was published that explored the hypothesis that the same set of genes may influence both migraine and depression (Schur et al., 2009). In this study, a genetic correlation was indeed reported, a finding we replicated in Chapter 7 of this thesis. Recently, a second study reporting shared genetic factors for migraine and depression was published (Stam et al., 2010). It is worth noting here that the presence of a genetic correlation does not tell us whether the association between two traits is caused by pleiotropy or by a causal mechanism. If the association between A and B is causal, genes that affect A will indirectly also affect B. To decide which hypothesis is more likely, additional information is necessary.

Interestingly, the Schur et al. study included a set of diagrams that showed the risk patterns in co-twins of individuals with migraine, depression, both, or neither. Although these diagrams were not created with the intention to investigate causality, they provide further evidence for a bidirectional causal relationship between migraine and depression. If the first twin had migraine only, the second twin did not have an increased risk of depression, unless they also had migraine, and vice versa. This risk pattern is similar to the pattern observed in Chapter 7 of this thesis, and that observed by Merikangas et al. (1993).

Together, these studies provide considerable evidence supporting the hypothesis of Merikangas et al., that migraine and depression are syndromically related. In other words, migraine might be viewed as part of a 'depression syndrome' in at least a subgroup of patients.

The hypothesis that in some patients, migraine and depression may be syndromically related, raises many new and important questions. For instance, is migraine really an aspect of depression, or is reporting migraine symptoms an aspect of depression? Is the relationship with depression specific to migraine, or

is there an equally strong relationship between depression and other somatic symptoms? Could it be that MDD patients simply overreport somatic symptoms as a result of their depressed mood?

While it is possible that the high prevalence of pain in depressed patients (in part) reflects a report bias, comorbidity of depression and chronic pain has indeed been reported in the literature (Bair et al., 2003). It has been suggested that chronic pain might in fact be a symptom of depression (Lépine & Briley, 2004). Moreover, there is a vast amount of literature that describes the effectiveness of various types of antidepressants in the treatment of headaches (see Tomkins et al. (2001) for a meta-analysis).

Genes for common migraine

What causes common migraine? The linkage study described in this thesis identified new potential regions of interest on chromosome 13 and 20, and replicated previous findings (e.g. the linkage peaks on chromosome 1 and 5), thus strengthening the confidence in these findings. One of our linkage peaks (on chromosome 20) was recently replicated by another group (Oedegaard et al., 2009).

This thesis presents the first meta-analysis of population-based genome-wide association studies on migraine. These analyses, which were based on data from six European cohorts, revealed some promising and plausible candidate genes for common migraine. The best result was found in the *NGFR* gene, which codes for the neural growth factor (NGF) receptor. Strong associations were also found in the *ATP1A2* gene, known to be involved in FHM. The combined results of the GWA meta-analysis and previous linkage studies supported the involvement of *GRID2*, which codes for a glutamate receptor. *GRID2* is located under a linkage peak on chromosome 4q22 that has been reported in several previous studies (Anttila et al., 2006; Bjornsson et al., 2003; Wessman et al., 2002). These promising findings suggest that GWA studies, when sufficiently large, can be quite effective for the identification of migraine genes and especially that combining results from studies using different gene-finding approaches is highly valuable.

Conclusions and implications

The results presented in this thesis, combined with the rapid developments in technology, hold great promise for future research. GWA studies have taught us that complex traits are often affected by large numbers of risk alleles with small effects (Visscher, 2008), which makes large study sizes a necessity. However,

large-scale genotyping will become easier and even more affordable in the future. In addition, the ever-growing sources of information regarding gene function, interactions and biological pathways will provide more tools to help us identify new genes that serve as candidates for migraine. This creates exciting new research opportunities, which will hopefully lead to the identification of actual disease variants, and a more complete understanding of the mechanisms that cause a migraine attack.

But technology is not the only factor that determines the success of gene-finding studies. An equally important aspect of finding genes for complex traits is the choice of a good phenotyping strategy. This is especially important given the potential genetic heterogeneity that may underlie the migraine phenotype. Even familial hemiplegic migraine (FHM), a monogenic disorder which follows a mendelian inheritance pattern, can be caused by dozens of different mutations in at least three different genes (de Vries et al., 2009). Given the complex nature of common migraine, genetic heterogeneity may be even more important in this trait. While the linkage study (Chapter 8) and GWA meta-analysis (Chapter 9) provide evidence for the involvement of one of the FHM genes in common migraine, it is likely that many more genes are involved.

A possible strategy to address the issue of genetic heterogeneity is to carefully document and account for any type of comorbidity in studies of migraine. The diagnostic criteria for migraine (Headache Classification Committee of the International Headache Society, 2004) state that migraine caused by another disorder should be classified as a secondary, rather than a primary headache. Indeed, in neurology, it is not uncommon to think of migraine as a phenomenon that occurs as a consequence of other (neurological) conditions. Examples are cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and retinal vasculopathy with cerebral leukodystrophy (RVCL), both disorders of which migraine is a prominent symptom (de Vries et al., 2009). In psychiatry, on the other hand, migraine is generally viewed as a disorder in itself, which happens to be highly prevalent in psychiatric patients (e.g., Cahill & Murphy, 2004). The possibility that it may actually be secondary to the psychiatric disorder is often neglected, even though it is not a strange thought, given that both neurological and psychiatric disorders are disorders of the brain.

Whether we classify a patient's migraine as a primary or a secondary headache has important implications for the assumptions we make about its etiology. Based on the findings in this thesis, it seems likely that migraine can

be secondary to anxiety and depression, and the same may be true for other psychiatric disorders, or even non-psychiatric comorbidities.

Therefore, it is important to carefully document any type of comorbid pathology in migraine patients. This should enable us to investigate which comorbid conditions are associated with migraine due to pleiotropy, and which conditions might have migraine as one of their symptoms. Furthermore, if all migraine patients were adequately screened for comorbid conditions, this might contribute to a more effective treatment of the migraine, for instance through treatment of the comorbid condition. Eventually, both research and treatment may benefit from such an approach.

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